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EXAMINER	
SCHMIDT,M	
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DATE MAILED: 09/20/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/886,313	Wright
Examiner	**Group Art Unit**
Schmidt	1635

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Response

A SHORTENED STATUTORY PERIOD FOR RESPONSE IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a response be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for response specified above is less than thirty (30) days, a response within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for response is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to respond within the set or extended period for response will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☒ Claim(s) 1-17, 30-31 is/are pending in the application.

Of the above claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-17, 30-31 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Notice of References Cited, PTO-892

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Interview Summary, PTO-413

☐ Notice of Informal Patent Application, PTO-152

☐ Other _____

Office Action Summary

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 4, 6-11, 16-17 and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4 and 17 are indefinite because it is not clear how the oligonucleotide, a nucleic acid sequence, "exhibits reduced dimer formation, reduced self-complementary interactions and reduced binding potential to the untranslated region." Although "reduced self-complementarity" may refer to an oligonucleotide sequence such as in reduced hairpin formation in a single stranded oligonucleotide, "dimer formation" implies two proteins binding. "Binding potential" in the instant case would appear to refer to protein binding to the oligonucleotide sequence. Therefore, it is not clear what structures and by what mechanism (protein-protein interaction versus a nucleotide-protein interaction for instance) the oligonucleotide is supposed to reduce and/or prevent.

Claims 6-11 and 16-17 are indefinite in view of the language "substantially free" because the metes and bounds of the sequence (ie. sequence range) used to define the scope of the region that is "substantially free of the coding sequence" can not be determined from such language.

Claim 30 is drawn to a synthetic oligonucleotide comprising two sequences of a consecutive segment of an untranslated 3' region of mRNA of a housekeeping gene linked together. It is not clear what the metes and bounds of 'linked together' are such that the structure of the claimed invention may be invisioned.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 12-17 and 31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

A. Claim 31 is drawn to a method of inhibiting the tumorigenicity of neoplastic cells resistant to hydroxyurea in a mammal by contacting the tumor with a growth inhibiting amount of at least one oligonucleotide having a sequence of a 3'UTR of mRNA of the R1 or R2 component of

ribonucleotide reductase protein R1 or R2 or the antisense sequences thereof or ribozymes comprising a sequence complementary to at least a portion of the UTR.

The specification as filed teaches in example 1 construction of RMP-6 cells lines (murine cell lines characterized as highly malignant) with vectors expressing the 3'UTR of R1 (SEQ ID No: 1), the 3'UTR of R2 (SEQ ID No: 2) or an empty control vector. Injection of syngeneic mice with these transformed cell lines demonstrated (1) reduced tumor weight with both R1 and R2 containing cell lines in comparison with the control line, suggesting tumorigenic suppression, and (2) ability of the R2 construct to suppress metastatic potential (characterized by suppress localization of the tumors to lung) but not with the R1 line. Further the transfection of human Hela cells with the murine R1 and R2 3'UTR sequences showed reduced cell growth over the control line in a cell count assay. Similar cell count assays were performed with specific regions of the 3'UTR R1 and R2 (the oligonucleotides of Tables 4 and 5) transfected into various human cancer cell lines (those in Tables 6 and 7) showing various levels of decreased cell growth over controls. Applicant therefore teaches inhibition of cancerous growth of metastatic cell lines via expression of murine 3'UTR R1 and R2.

The specification as filed, teaching some *ex vivo* application to mice of metastatic cells containing vector constructs expressing the 3'UTR sequences of murine R1 or R2, does not reasonably teach one skilled in the art success of reduced tumorigenicity of any neoplastic cell(s) or whole organisms via application of the 3'UTR sequences of any housekeeping gene as broadly claimed. The specification does not provide any sequence structure or application of other 3'UTR

nucleotide sequences for therapeutic purposes to any other whole organism as broadly claimed. The teaching of some reduced tumorigenicity and reduced metastatic potential with murine 3'UTR R1 and R2 does not reasonably provide enablement for any application of any 3'UTR sequences to any whole organism as broadly claimed for treatments involving reduced tumorigenicity and reduced metastatic potential. The additional teaching of reduced cell growth of human carcinoma cell lines upon transfection with the whole or partial sequence of the 3'UTR of R1 and R2 does not provide reasonable correlation to success (ie. treatment) in any whole organism, including human, as broadly claimed. Further, the specification does not teach any specific antisense or ribozyme sequences for therapeutic applications and therefore neither is it enabling for design of such compositions for application to whole organisms as broadly claimed.

There is a high level of unpredictability in gene therapeutic art for applications of oligonucleotide sequences and/or expression of nucleic acid sequences in cells in whole organisms. The factors considered unpredictable for expression of gene therapeutic application of nucleic acid compositions to a whole organism are taught by Anderson (1998). He teaches the unpredictable nature of such treatments as stemming from "problems that investigators face in developing retroviral vectors that are effective in treating disease..., obtaining efficient delivery, transducing non-dividing cells, (and) sustaining long-term gene expression." He ascribes these difficulties to all forms of gene therapy delivery: *in vivo*, *ex vivo* and *in situ* (page 25). Further Crystal teaches the unpredictability of correlation between gene therapeutic successes in murine models and related therapeutic successes in other whole organisms such as humans (p. 409).

Anderson and Crystal both teach a general lack of guidelines in the art for general success of gene therapeutic applications since it is unpredictable to administer vector or oligonucleotide nucleic acid compositions which will target intended cell(s), retain sustained expression of such therapeutic constructs, and further since isolated successes with a particular construct in one organism do not teach an expectation of success in another whole organism.

In the instant case the factors not taught by the specification nor generally taught in the art are (1) the sequences of other 3'UTR regions of housekeeping genes other than murine R1 or R2 having the capacity to decrease tumor size *in vivo* as would be necessary for treatment of a mammal, (2) the correlation between murine R1 or R2 3'UTR expression in murine or human metastatic cells *in vitro* and treatment effects, ie. reduced tumorigenicity, in a whole organism, (3) correlation between the decreased tumorigenicity observed in the syngeneic mice upon *ex vivo* application of a specific murine cell line (RMP-6) expressing 3'UTR R1 or R2 sequences and treatment effects of reduced tumorigenicity (and/or reduced metastatic potential as observed with the 3'UTR R2 expressing cells), in any other mammal whole organism. Although the specification teaches reduced cell growth *in vitro* with the murine 3'UTR R1 and R2 sequences, and it is generally known in the art that murine gene sequences can share high homology with human gene sequences, no evidence of success of any reduced tumorigenicity in a human whole organism is taught. Due to the unpredictabilitity in the art discussed above, there is no expectation of success of reduced tumorigenicity in humans via gene therapeutic administration of murine 3'UTR R1 or R2 sequences as shown in mice.

The lack of guidance in the specification as filed for any modulation, or more specifically reduction, of tumorigenicity of neoplastic cells in a mammal via administration of 3'UTR sequences of any housekeeping gene as broadly claimed coupled with the high level of unpredictability in the art for any gene therapeutic application of a nucleic acid constructs to a whole organism would necessarily lead one of skill in the art to practice an undue amount of experimentation.

Further the specification as filed reads broadly on application of any antisense or ribozyme sequence designed to inhibit any 3' UTR sequence from any housekeeping gene and further treatment effects when administered either alone or in combination with any 3'UTR housekeeping oligonucleotide as broadly claimed. However, the specification as filed only suggests application of any antisense or ribozyme sequences. The specification does not teach design of any specific antisense or ribozyme sequences nor application to cells in culture or whole organisms either alone or in combination with 3'UTR housekeeping gene oligonucleotides (see the 35 USC 112, first paragraph, written description rejection above).

There is a high level of unpredictability known in the antisense art for design and application of antisense and/or ribozymes to whole organisms. The factors considered barriers to successful delivery of antisense delivery to the organism are: (1) penetration of the plasma membrane of the target cells to reach the target site in the cytoplasm or nucleus, (2) withstanding enzymatic degradation, and (3) the ability to find and bind the target site and simultaneously avoid

non-specific binding (see Branch). Despite the synthesis of more resilient, nuclease resistant, oligonucleotide backbones and isolated successes with antisense therapy *in vivo*, the majority of designed antisense molecules still face the challenge of successful entry and localization to the intended target and further such that antisense and other effects can routinely be obtained. Flanagan teaches, "oligonucleotides (in vivo) are not distributed and internalized equally among organs and tissues.... Unfortunantly, therapeutically important sites such as solid tumors contain very little oligonucleotide following intravenous injections in animals (page 51, column 2)." *In vitro*, antisense specificity to its target may be manipulated by "raising the temperature or changing the ionic strength, manipulations that are commonly used to reduce background binding in nucleic acid hybridization experiments." (Branch, p. 48) Discovery of antisense molecules with "enhanced specificity" *in vivo* requires further experimentation for which no guidance is taught in the specification. Note Branch who teaches the state of the art for designing an antisense which inhibits a target *in vivo:* it "is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells (Branch, p.49)." And in the instant case, the claims read broadly on administration of an antisense or ribozyme inhibitors in any cell, therefore the whole organism included. No evidence of design nor application of successful antisense or ribozyme sequences either alone or in combination for the functions claimed have been shown.

One of skill in the art would not accept on its face the successful design and delivery of any antisense or ribozyme molecules for the housekeeping sequences broadly claimed for applications *in vivo* and further, treatment effects, in view of the lack of guidance in the specification and the unpredictability in the art as cited above. Neither the specification nor the technology today teach general guidelines for successful design or delivery for treatment effects of antisense, ribozyme or the possible combinations of such molecules and oligonucleotides in whole organisms. Specifically the specification does not teach (1) design or stability of the antisense, ribozyme or combinations thereof *in vivo*, (2)effective delivery to the whole organism and specificity to the target tissues, (3) dosage and toxicity, nor (4) entry of molecule into cell and effective action therein marked by visualization of the desired treatment effects of the claimed active compositions. These key factors are those found to be highly unpredictable in the art as discussed *supra*. The lack of guidance in the specification as filed for these factors would therefore require "trial and error" experimentation beyond which is taught by the specification as filed. Therefore, it would require undue experimentation to practice the invention as claimed. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of all the unpredictable factors argued above for which neither the specification as filed nor the art provide any particular guidance or guidelines.

B. Claims 12-17 are drawn to pharmaceutical compositions of the oligonucleotides of claim 1 and compositions having antisense, ribozyme or a combination of such nucleic acid sequences.

The use of the phrase "pharmaceutical composition" implies *in vivo* treatment of a patient. The factors considered unpredictable are those taught by Anderson (see above) for gene therapy applications of oligonucleotides and those taught by Branch (see above) for antisense and ribozyme delivery issues to whole organisms. The specification does not teach the formulation of such pharmaceutical compositions for successful application of the composition to the desired target(s). The quantity of experimentation required to practice the invention as claimed would require determination of the structures of antisense and/or ribozyme or oligonucleotide sequences, determination of mode(s) of delivery, formulation, dosage, toxicity etc. for desired treatment effects.

The lack of guidance in the specification as filed for the unpredictable factors argued above coupled with the unpredictability in the art for gene therapeutic application of polynucleotide constructs (see above) would necessarily lead one skilled in the art to practice an undue amount of experimentation to make and use the invention as broadly claimed.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1-7 and 9-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Pavloff et al.

Pavloff et al. teach the full length gene sequences of murine and human R1 and R2 ribonucleotide reductase (see figure 2), including the 3'UTR sequences of applicants SEQ ID NOS 1 and 2. They further teach specific oligonucleotide portions of the 3'UTRs and/or coding regions. The open "comprising" language of claim 1 allows the whole gene sequences taught by Pavloff et al. to read on claim 1 since the whole sequence taught by Pavloff et al. encompasses the untranslated region (5' and/or 3' sequence) of the housekeeping gene ribonucleotide reductase.

Thus Pavloff et al. anticipates the claimed invention.

7. Claims 1-3 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Amara et al.

Amara et al. teach the sequence of R2 ribonucleotide reductase 3'UTR (see abstract). They specifically teach oligonucleotides (including synthetic olignonucleotides) comprising regions of the 3'UTR of human and murine R2 (p. 1463 and p. 1465), and vectors expressing such sequences. They teach probes to the 3'UTR of R2 (see page 1465). They also teach binding studies, ie. screening assays, for identification of proteins binding to regions of the 3'UTR for correlated regulation of the R2 gene sequence with Tgf-beta1 expression having suggested roles in cell proliferation.

Thus Amara et al. anticipates the claimed invention.

8. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Voss et al.

Claim 1 is draw to oligonucleotides comprising an untranslated region of any housekeeping gene.

Voss et al. teach the sequence, including untranslated region of human casein kinase II subunit beta, a housekeeping gene, and vectors expressing such sequence. The sequence taught by Voss et al. reads on claims 1, 17 and 18 since the open "comprising" language of claim 1 encompasses the whole gene sequence including the untranslated regions.

Thus Voss et al. anticipates the claimed invention.

9. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Hilfiker et al.

Claim 1 is drawn to oligonucleotides comprising an untranslated region of any housekeeping gene.

Hilfiker et al. teach the sequence including the untranslated region of human plasma membrane calcium pump isoform 1, a housekeeping gene, and vectors expressing such sequence. The sequence taught by Hilfiker et al. reads on claim 1 since the open "comprising" language of claim 1 encompasses the whole gene sequence including the untranslated regions.

Thus Hilfiker et al. anticipate the claimed invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *George Elliott, Ph.D.* may be reached at (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

M. M. Schmidt
September 11, 2000

ROBERT A. SCHWARTZMAN
PRIMARY EXAMINER